Smad1&5 but not Smad8 establish stem cell quiescence which is critical to transform the premature hair follicle during morphogenesis towards the Postnatal State.

Journal: Stem Cells

Publication Year: 2013

Authors: Eve Kandyba, Virginia M Hazen, Agnieszka Kobielak, Samantha J Butler, Krzysztof Kobielak

PubMed link: 24023003

Funding Grants: CIRM Stem Cell Biology Training Program

Public Summary:
Hair follicles (HFs) are regenerative mini-organs that offer a highly informative model system to study the regulatory mechanisms of hair follicle stem cells (hfSCs) behavior. Our previously published findings (JCB 2003, PNAS 2007, PNAS 2013) demonstrated that inhibition of Bone morphogenetic protein (BMP) signaling is essential for promoting the activation of resting bulge SCs to proliferation and SC progeny to properly differentiate into hairs. However, there is still a gap in our scientific knowledge regarding precisely how BMP signaling relays the signals from the BMP receptor and whether it is mediated by the canonical or non-canonical pathway. We addressed this question by examining the role of two components of BMP signaling, Smad1 and Smad5, during hair development and postnatal hair cycling in skin in vivo. We demonstrated that BMP signaling operates predominantly via canonical pathway components and operates differently during development and in mature adult skin causing different phenotypic outcomes. We discovered that Smad-deficient HFs could not form a mature hfSCs population. We showed that maturation of bulge SCs by active canonical BMP signaling through pSmad1 and pSmad5 is a critical event in hair development to promote pSmad8 activity in postnatal HFs. Thus, when we deleted Smad1 & Smad5 in adult hfSCs once HFs had fully matured, we found that growing Smad-deficient HFs could generate visible hair at the skin surface. Collectively, our findings suggest a pivotal role for BMP-Smad signaling demonstrating distinguished non-overlapping functions of pSmad8 with pSmad1 and pSmad5 in hfSCs regulation and HF development but a redundant role in adult HF regeneration and hair shaft production.

Scientific Abstract:
Hair follicles (HFs) are regenerative mini-organs that offer a highly informative model system to study the regulatory mechanisms of hair follicle stem cells (hfSCs) homeostasis and differentiation. Bone Morphogenetic Protein (BMP) signaling is key in both of these processes, governing hfSCs quiescence in the bulge and differentiation of matrix progenitors. However, whether canonical or non-canonical pathways of BMP signaling are responsible for these processes remains unresolved. Here, we conditionally ablated two canonical effectors of BMP signaling, Smad1 and Smad5 during hair morphogenesis and postnatal cycling in mouse skin. Deletion of Smad1 and Smad5 (dKO) in the epidermis during morphogenesis resulted in neonatal lethality with lack of visible whiskers. Interestingly, distinct patterns of phospho-Smads (pSmads) activation were detected with pSmad8 restricted to epidermis and pSmad1 and pSmad5 exclusively activated in HFs. Engraftment of dKO skin revealed retarded hair morphogenesis and failure to differentiate into visible hair. The formation of the pre-bulge and bulge reservoir for quiescent hfSCs was precluded in dKO HFs which remained in prolonged anagen. Surprisingly, in postnatal telogen HFs, pSmad8 expression was no longer limited to epidermis and was also present in dKO bulge hfSCs and matrix progenitors. Although pSmad8 activity alone could not prevent dKO hfSCs precocious anagen activation it sustained efficient postnatal differentiation and regeneration of visible hairs. Together, our data suggest a pivotal role for canonical BMP signaling demonstrating distinguished non-overlapping function of pSmad8 with pSmad1 and pSmad5 in hfSCs regulation and hair morphogenesis but a redundant role in adult hair progenitors differentiation. Stem Cells 2013.

Source URL: https://www.cirm.ca.gov/about-cirm/publications/smad15-not-smad8-establish-stem-cell-quiescence-which-critical-transform